Breast cancer and PTEN

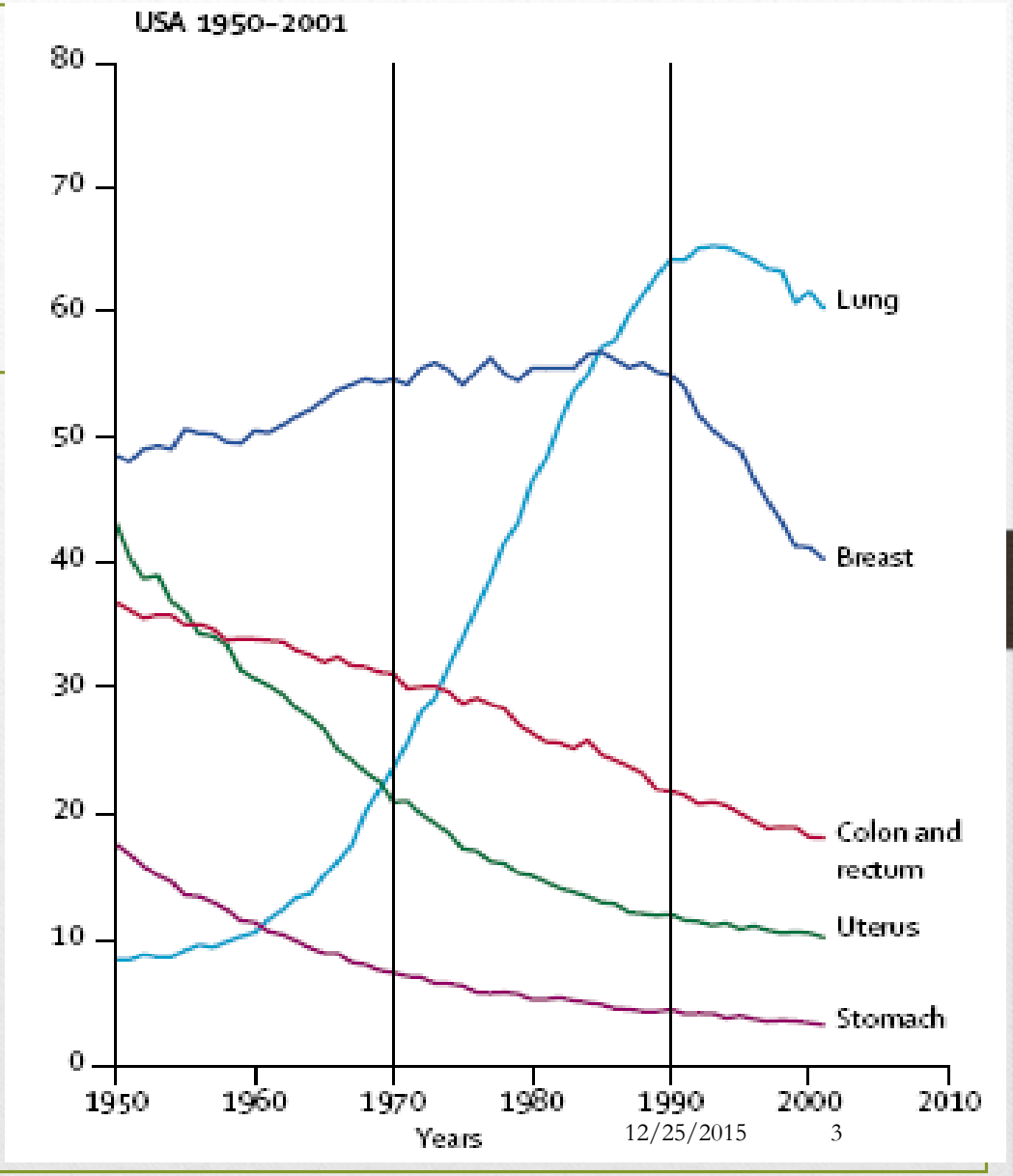
Majid hosseini
Biotechnology
Under supervision : Dr Gheibi

Breast cancer is second only to lung cancer as a cause of cancer deaths in American women

- One out of every eight women will be diagnosed with breast cancer in 2011
- Fortunately, radical mastectomy (surgical removal) is rarely needed today with better treatment options

Trends since 1950 in age-standardized death rates comparing breast and selected other types of cancer, among women in the USA

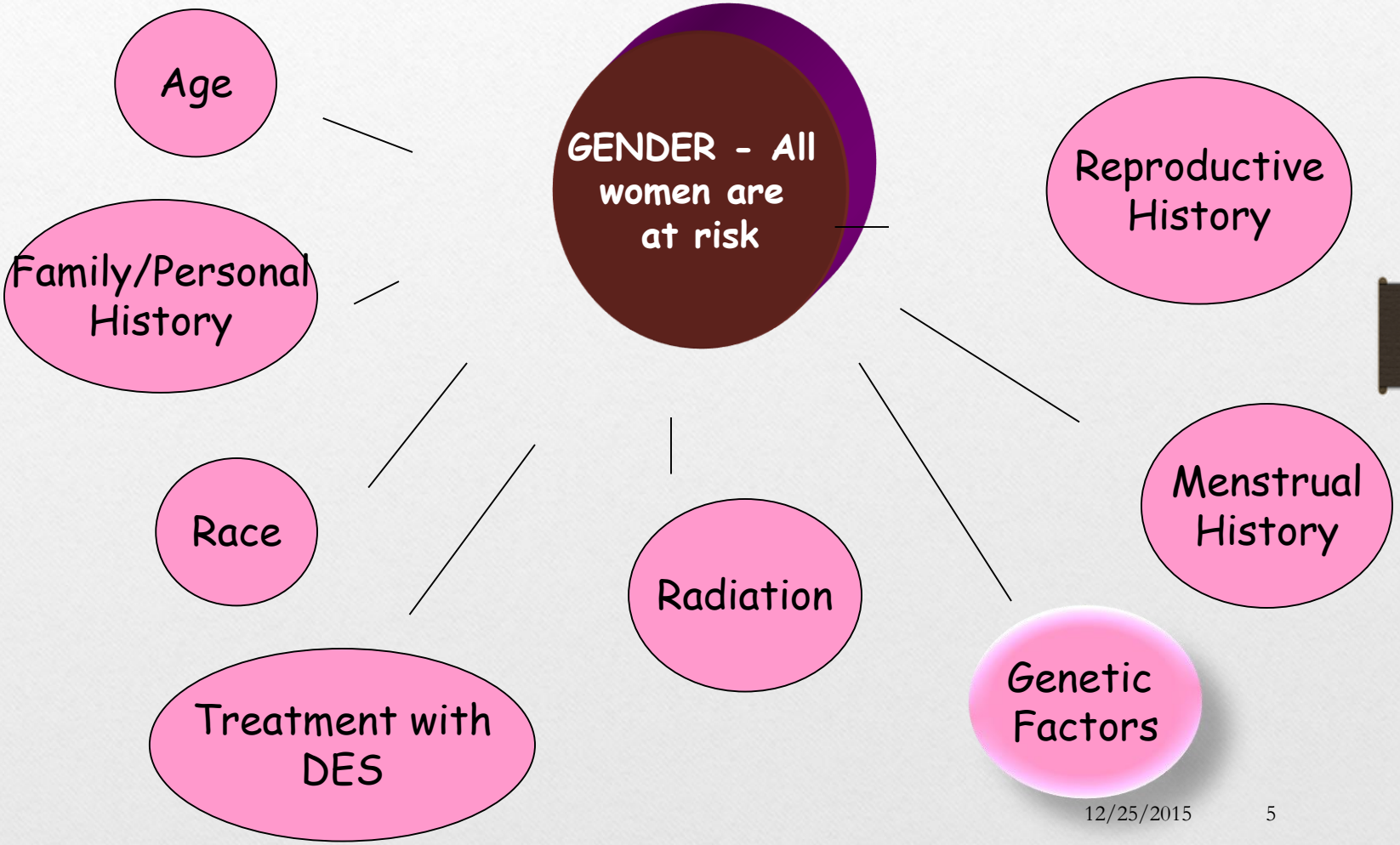
EBCTCG, Lancet, 2010



BREAST CANCER IN THE WORLD

- 1.15 million new cases
- Incidence increasing in most countries
- 470 000 deaths
- Half of the global burden in low- and medium-resourced countries

Breast Cancer Risk Factors unalterable factors



Cancer predisposition genes associated with breast cancer

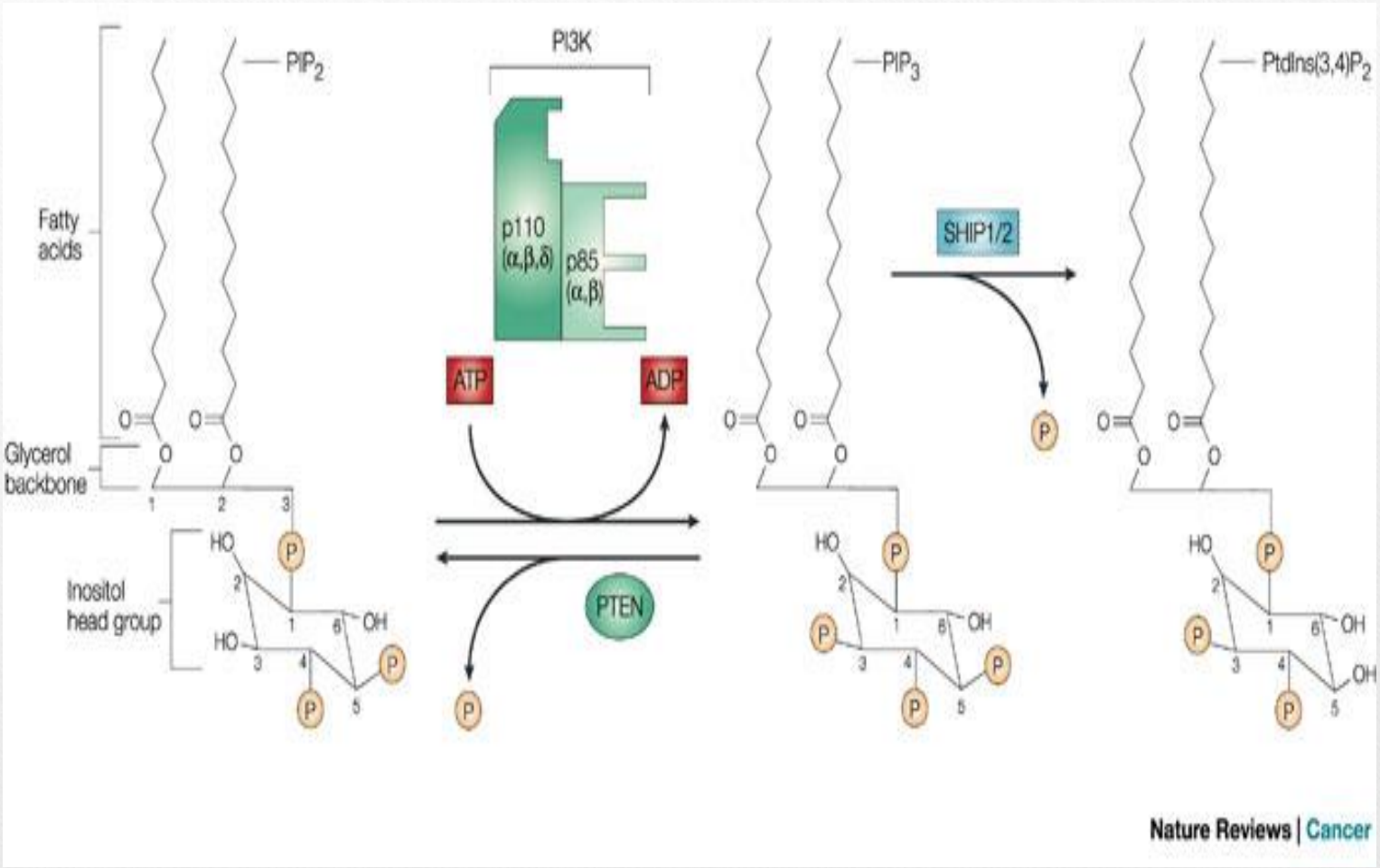
Gene (chromosome)	Penetrance	Clinical features
BRCA1 (17q21)	High	Breast and epithelial ovarian cancers
BRCA2 (13q12-13)	High	Breast and epithelial ovarian cancers
PTEN (10q23.3)	High	Cowden syndrome
TP53 (17q13.1)	High	Li-Fraumeni syndrome
RAD51C (17q23)	High (?)	Breast and epithelial ovarian cancers; Fanconi anemia (subtype-O; biallelic mutation)
CDH1 (16q22.1)	Moderate	Gastric cancer and lobular breast cancer
ATM (11q22.3)	Moderate	Ataxia-teleangectasia (biallelic mutation)
CHEK2 (22q12.1)	Low	Some association with Li-Fraumeni syndrome
BRIP1 (17q22)	Low	Fanconi anemia (biallelic mutation)
PALB2 (16q12)	Low	Fanconi anemia (biallelic mutation)
KRAS-variant (12p12.1)	Unknown	Breast cancer, epithelial ovarian, lung cancer, head and neck cancers, GI cancer

PTEN is a tumor suppressor gene that is essential for embryonic development

- **PTEN gene located on Chrom 10 (10q23)**
- **Several different Pten null mice lines were generated-produced varying results depending upon which genetic background of mouse was used (e.g.129SvEv vs. C57Bl6)**
- **But in all cases mice do <u>NOT</u> survive to birth ∴ <u>PTEN required for embryogenesis</u>**

PTEN is a key player in some human diseases

- Cowden Disease (CD),Lhermitte-Duclos Disease (LDD),Bannayan-Zonana Syndrom (BZS)
- In all 3 disorders, germline mutations in PTEN have been observed
- Still unclear why mutation in one gene leads to 3 related yet distinct disorders
- An increased risk of breast cancer has been reported among men with Cowden syndrome, with women with Cowden syndrome having an approximate 75% risk for benign breast disease, as well as an over 50% lifetime risk for breast cancer


PIP2
PI3K
PIP3
PtdIns(3,4)P2
Fatty acids
p110 (α,β,δ)
p85 (α,β)
SHIP1/2
ATP
ADP
Glycerol backbone
Inositol head group
PTEN
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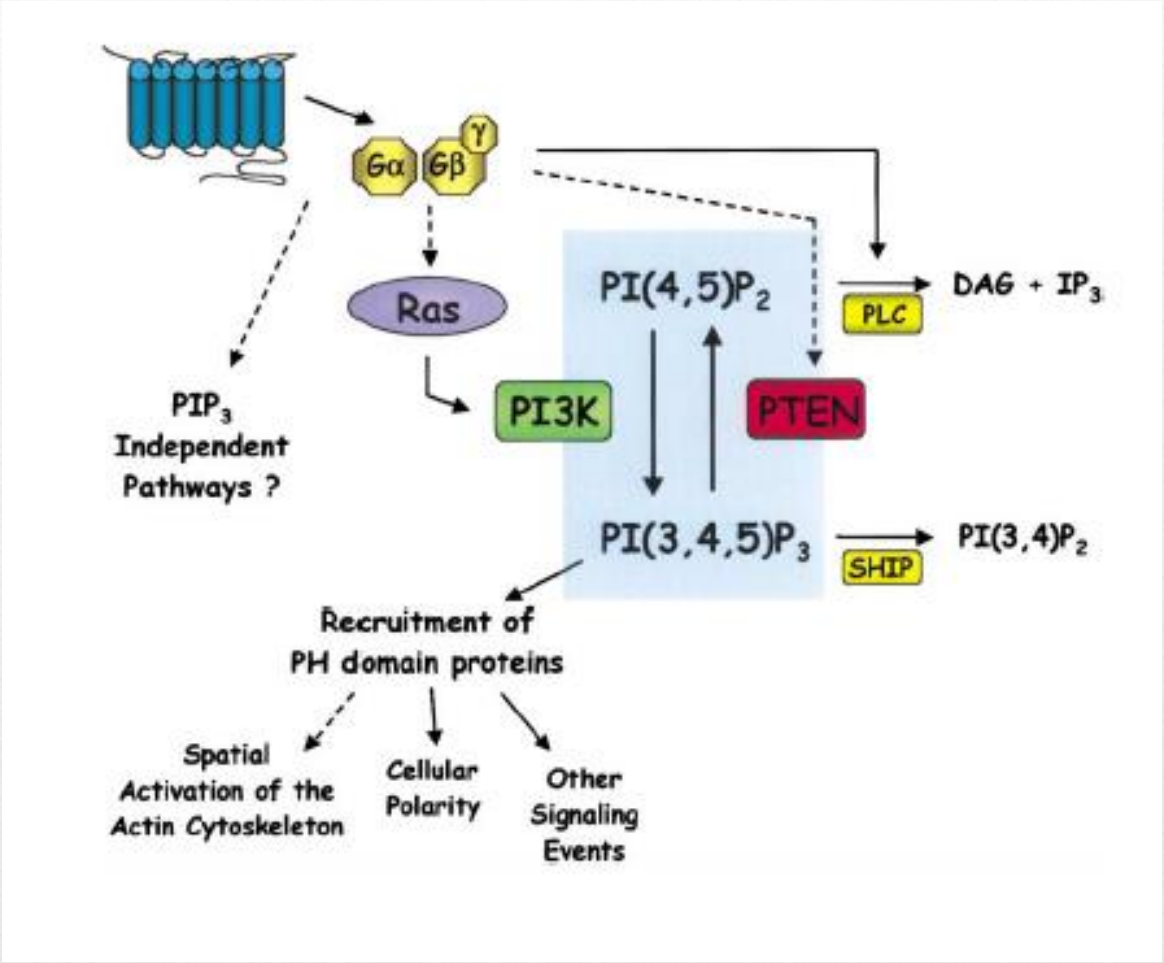
PTEN and PI-3 Kinase act as antagonists in signaling



PTEN (Phosphatase and Tensin homolog deleted on chromosome Ten)

- The PTEN protein can dephosphorylate phosphatidyl inositol 3,4,5 trisphosphate and thereby antagonize the phosphatidylinositol-3-kinase signaling pathway.

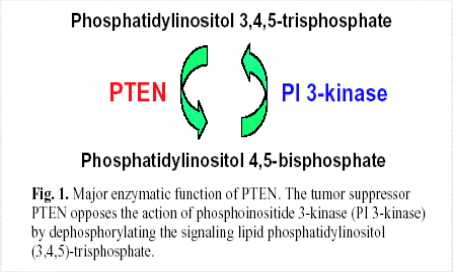


Fig. 1. Major enzymatic function of PTEN. The tumor suppressor PTEN opposes the action of phosphoinositide 3-kinase (PI 3-kinase) by dephosphorylating the signaling lipid phosphatidylinositol (3,4,5)-trisphosphate.

- PTEN negatively regulates intracellular levels of phosphatidylinositol-3,4,5-trisphosphate in cells and functions as a tumor suppressor by negatively regulating AKT/PKB signaling pathway.

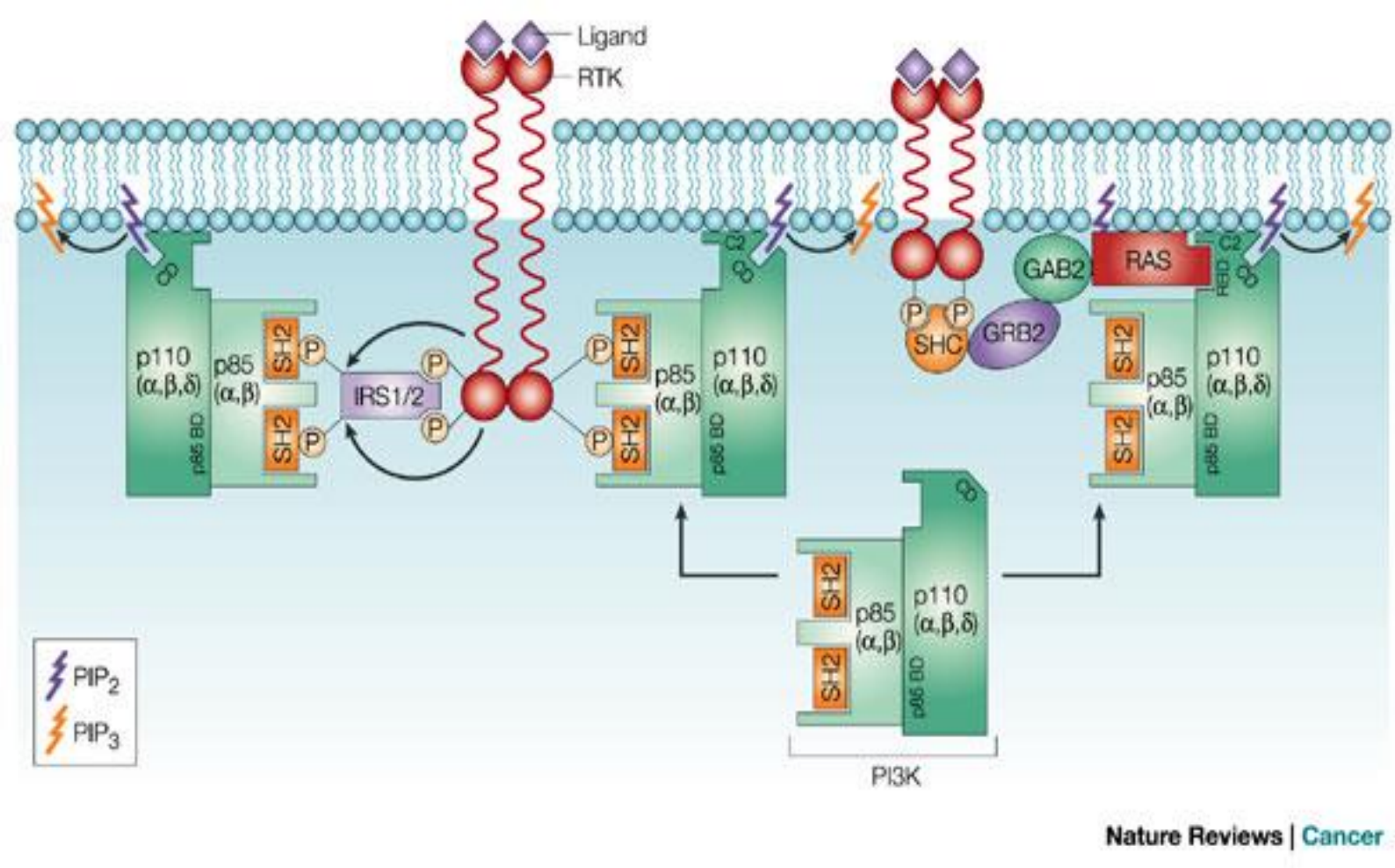
- PTEN may also inhibit cell migration through protein phosphatase activity on a threonine phosphate residue.

- Reference: Raftopoulou et al. Science 303, 1179-1181 (2004).

Relationship of PTEN and Akt

- it appears that one of the most relevant consequences of the PTEN-defective phenotype is the activation of the PI3K/Akt signaling pathway.

- Akt mediates multiple intracellular functions pertaining to cell proliferation and apoptosis and has been implicated in chemoresistance in colon, bladder ,ovarian and breast cancers


Ligand
RTK
p110 (α,β,δ)
p85 (α,β)
SH2
P
IRS1/2
GAB2
RAS
SHC
GRB2
C2
RBD
p85 BD
PIP2
PIP3
PI3K
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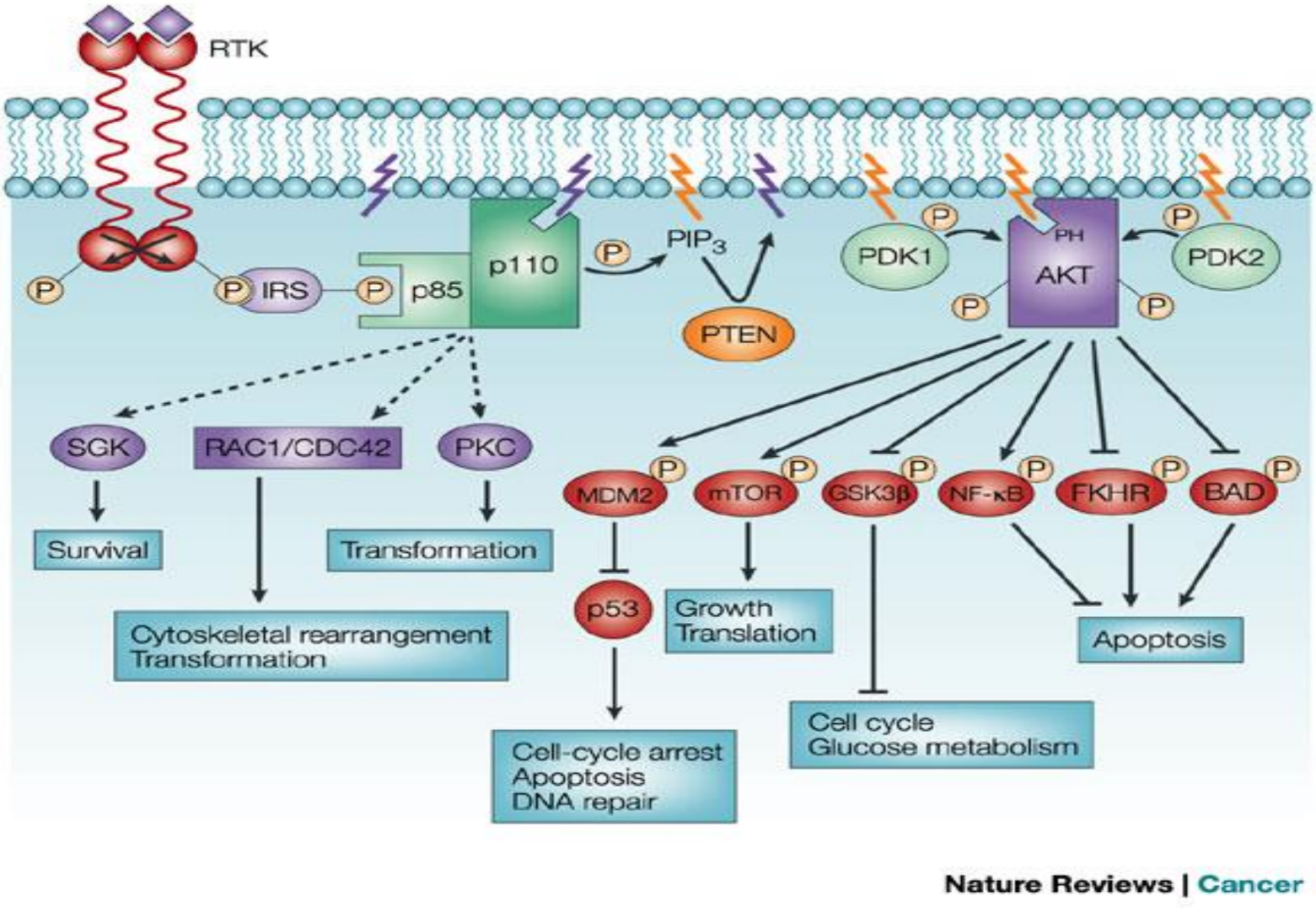
RTK
P
IRS
P
p85
p110
P
PIP3
PTEN
PDK1
P
PH
AKT
P
P
PDK2
P
SGK
RAC1/CDC42
PKC
Survival
Transformation
Cytoskeletal rearrangement
Transformation
MDM2
P
mTOR
P
GSK3β
P
NF-κB
P
FKHR
P
BAD
P
p53
Growth
Translation
Apoptosis
Cell-cycle arrest
Apoptosis
DNA repair
Cell cycle
Glucose metabolism
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HONG-YAN Research

- 146 female Chinese patients, who were diagnosed with breast cancer between 2003 and 2006
- Polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) analysis was performed to analyze mutations of the PTEN gene
- The positive expression rate of PTEN was 57.5% (84/146) in the breast cancer patients, but 100% in the normal breast tissues closely adjacent to the carcinoma

L. Fulcher Research

- MCF-7, MDA-MB-435 and MDA-MB-68 breast cancer cell lines
- MCF-7 cell lines were transfected with the antisense PTEN constructs
- determine the relationship between PTEN status and response to inhibitors of the PI3K/Akt kinase pathway
- PTEN expression strongly correlates with cellular response to exposure to PI3 kinase pathway inhibitors

Summary

- The breast is a dynamic organ- undergoes cyclical proliferative changes throughout life under the influence of hormones and growth factors- so may be likely to be more altered by environmental carcinogens

- Key function for ER and PR in breast cells. The same hormones that are important for breast growth during pregnancy are also important for breast cancer.

- ER function in signaling through other growth factor receptor pathways becomes very important in cancer. Production of estrogen through alternate sources keeps E supply ongoing in postmenopausal women.

Summary

- PTEN is both a lipid and protein phosphatase
- Shown to be involved in pathways that involve apoptosis (or anoikis), mobility, and cell adhesion
- PTEN is necessary for embryogenesis and may also control tumor development in mice
- PTEN involved in 3 major genetic diseases with mutations in one gene that cause similar yet distinct phenotypes
- PTEN mutated in many cancers but more needs to be learned about the pathways involved to better understand how cancers arise and to determine how to design new therapeutic treatments

TUMOR-SUPPRESSOR GENES - Suggested reading

- **B.H. Park and B. Vogelstein, In Holland-Frei Cancer Medicine 6th Edition, Part II, Section 1, 7. Tumor-Suppressor Genes, 2003.**

- **Robert Weinberg, The Biology of Cancer, Chapter 7, Garland Press, 2007.**

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- 2. Waite KA, Eng C. Protean PTEN: form and function. Am J Hum Genet. 2002;70:829–844.[PMC free article] [PubMed]
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